



Hot Topics in Pediatric A/I: Atopic Dermatitis

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Disclosures: Lynda Schneider, MD

Astellas – Investigator

NIH/NIAID/DAIT (Atopic Dermatitis Vaccinia Network and Atopic Dermatitis Research Network)

This presentation will include discussion of OFF LABEL uses
tacrolimus ointment, fluticasone cream/ointment.

Learning Objectives:

- Describe the most recent clinical research findings in pediatric eczema
- Apply recent advances in pediatric allergy/immunology

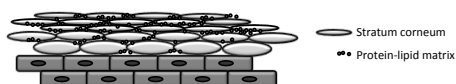
Outline

- Atopic Dermatitis
 - Pathology/Genetics
 - Vitamin D
 - Treatment
 - Mental health
 - Predictors of Success
 - Practice Parameters



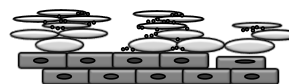
What goes wrong in AD?

Normal epidermis: a protective barrier



- The stratum corneum: a protein-lipid matrix with filaggrin, ceramide, and sphingosine
 - Barrier against water loss and allergen/microbe entry

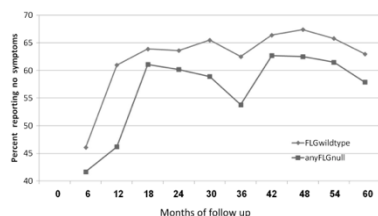
Defect in Epidermal Barrier Function in AD



- **Filaggrin** loss-of-function mutations (R501X and 2282del4): associated with ↑ risk of AD, asthma associated with AD
- US PEER study
 - 27.5% Caucasians
 - 5.8% AA

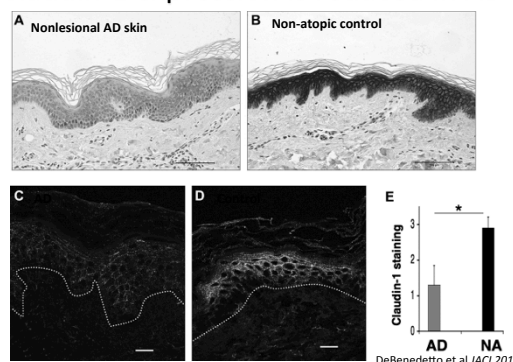
Palmer CN et al. *Nature Genetics*, 2006; Weidinger S et al. *JACI*, 2008
Margolis DJ, Andrea J. Apter, *JACI* 2012;131: 912-917

The persistence of AD and filaggrin (FLG) mutations in a US longitudinal cohort



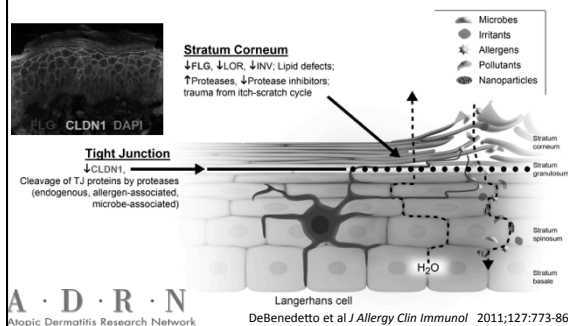
Margolis DJ, Andrea J. Apter, Journal of Allergy and Clinical Immunology 2012;131: 912-917.

Claudin-1 expression is reduced in AD



DeBenedetto et al JACI 2011

Stratum Corneum + Tight Junctions 2 barrier structures



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Atopic Dermatitis Research Network

DeBenedetto et al J Allergy Clin Immunol 2011;127:773-86

Clinical Implications

Atopic Dermatitis: A Practice Parameter Update 2012

- **Summary statement 4.** The clinician should know that atopic dermatitis has become widely accepted as a **disorder that is at least in part initiated by skin barrier defects**. These barrier defects can be acquired or genetic.
- **Summary statement 12.** The clinician should be aware that atopic dermatitis is characterized by **reduced skin barrier function**, which leads to enhanced water loss and dry skin; therefore the clinician should recommend **hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer.** (D)

Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, et al. J Allergy Clin Immunol. 2013 Feb; 131:

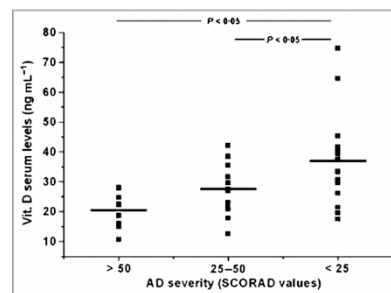
Correlation between serum 25-hydroxyvitamin D levels and severity of AD in children

- Evaluate if low levels of vitamin D correlate with the severity of AD
- 37 children ages 8 mos to 12 years with AD enrolled at University of Verona in Verona, Italy
- Severity determined by SCORAD (Severity Scoring of AD)



Peroni DG et al British Journal of Dermatology
Volume 164, Issue 5, pages 1078-1082, 11 APR 2011

Correlation between serum 25-hydroxy vitamin D levels and severity of atopic dermatitis in children



British Journal of Dermatology
Volume 164, Issue 5, pages 1078-1082, 11 APR 2011 DOI: 10.1111/j.1365-2133.2010.10147.x

Pilot study of 1000 IU Vitamin D for AD in eleven Boston children

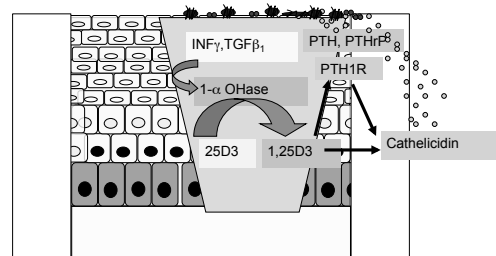
in winter

Change in IGA score	Vitamin D	Placebo	Total
+ 1 (worse)	-	1 (17%)	1
0 (same)	1 (20%)	4 (67%)	5
- 1 (better)	4 (80%)*	1 (17%)	5
Total	5	6	11

*p<0.05

Ref. Sidbury R, et al. British Journal of Dermatology. 2008;159(1):245-7.

Local conversion of Vitamin D in skin drives AMP expression



A · D · R · N
Atopic Dermatitis Research Network

Schauber et al. JCI 2006
Liu et al. Science 2006
Muehleisen B et al. Science Transl Med 2012

Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults

	FokI	BsmI	Apal	TaqI	Control (%) n=264	AD (%) n=265	P-value	Permutated P-value	Severe AD (%) n=148	P-value	Permutated P-value
C	A	A	C	C	26.6	21.2	0.040	0.11	19.9	0.028	0.07
T	G	C	T	T	19.0	21.9	0.24	0.64	24.9	0.06	0.16
	G	C	T	T	44.6	49.8	0.09	0.42	54.7	0.005	0.011
	A	A	C	C	41.0	34.5	0.030	0.75	32.4	0.016	0.052

Heine G et al British J Dermatol; 2013:in press

Clinical Implications

Atopic Dermatitis: A Practice Parameter Update 2012

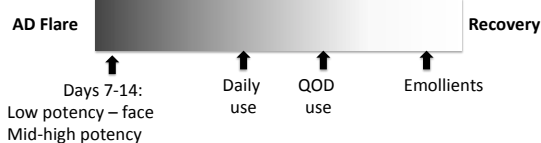
Vitamin D

- Summary statement 29. Patients with atopic dermatitis may benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, et al. J Allergy Clin Immunol. 2013 Feb; 131:295-9.

Anti-inflammatory Treatment

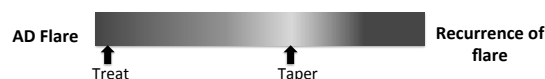
Topical Steroid Application



Aim for RARE FLARES

Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, et al. Atopic Dermatitis: A Practice Parameter Update. J Allergy Clin Immunol. 2013 Feb; 131:295-9.
Krakowski AC, Eichenfield LF, Dohil MA. Pediatrics 2008 Oct 122(4):812-24

For patients with frequent flares



Proactive (OFF LABEL) usage 2 to 3 times weekly to areas typically affected by AD

- Fluticasone propionate cream or ointment
- Topical tacrolimus

Wollenberg A et al Allergy 2008;63:742-750; Paller AS et al Pediatrics 2008;122: e1210-e1218
Breneman D et al J Am Acad Dermatol 2008;58:990-9; Thaci D et al Br J Dermatol 2008 Dec;159(6):1348-56

Proactive treatment of eczema (OFF LABEL)

- **Cost-effectiveness of tacrolimus ointment : twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective.**
- Healy E, et al. British Journal Derm 2011 164:387-95.
 - Twice weekly maintenance more cost effective than standard twice daily reactive treatment

Proactive treatment of eczema (OFF LABEL)

- Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials.
- Schmitt J et al. British Journal Derm 2011 164:387-95
 - Fluticasone propionate and tacrolimus are more efficacious to prevent AD flares than vehicle
 - Fluticasone may be more efficacious than tacrolimus although study designs differ
 - 4.5% of children in one fluticasone study showed biochemical evidence of adrenal suppression
- Clinical Implications: Consider proactive therapy

Mental Health Comorbidity in AD

- Cross sectional study comparing No eczema to children with eczema
- 2007 National Survey of Children's Health
- Questionnaire to parents
 - told by health care provider your child has
 - Eczema
 - ADD or ADHD
 - Depression
 - Anxiety
 - Behavior or conduct disorder problem
 - Autism
 - Parental description of severity of eczema



Yaghamie P, et al. J Allergy Clin Immunol 2013;131:428-33.

Mental Health Comorbidity in AD

- Mental health care usage
 - No eczema 7.89%
 - Eczema 12.12%
 - $P < .0001$
- Mean number of days of adequate sleep decreases as eczema severity increases
 - No eczema 6.09
 - Eczema 5.22
 - $P < .0001$



Yaghamie P, et al. J Allergy Clin Immunol 2013;131:428-33.

Mental Health Comorbidity in AD

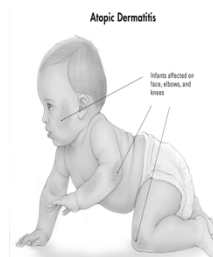
Mental health condition	No Ecz		Eczema		Eczema		P value
	Ref	Mild	Mod	Sev	Sev	P value	
ADHD	1.00	1.66	<0.001	1.76	.0004	4.35	<.0001
Anxiety	1.00	1.44	.09	2.18	.0006	2.81	.03
Depression	1.00	1.64	.08	2.02	<.0097	2.12	.22
Conduct disorder	1.00	1.59	.0068	1.82	.0159	3.90	.0016
Autism	1.00	1.78	.0159	3.25	.0003	7.41	<.0001

aOR, Adjusted odds ratio.

Yaghamie P, et al. J Allergy Clin Immunol 2013;131:428-33.

Infant eczema, sleeping problems and mental health at 10 years of age

- Prospective population based cohort study in Germany (LISA-plus)
- Relationship between eczema within the first 2 years, infant sleeping problems and mental health at 10 years
- Logistic regression modeling



Schmitt J, et al. Allergy 2011;66:404-11

Infant eczema, sleeping problems and mental health at 10 years of age

- 1578 children with complete info
- 266 (24%) had physician diagnosed eczema within the first 2 years
- 92 (6%) had sleep problems due to pruritus
- 1162 never had eczema nor sleep problems



Schmitt J, et al. Allergy 2011;66:404-11

Infant Eczema, Sleeping Problems and Mental Health at 10 yrs. of age

Variable	Odds Ratio (95% CI)
• Emotional problems	
– Infant sleep problems	2.40 (1.32 – 4.39)
– Infant eczema with sleep problems	2.63 (1.20 - 5.78)
• Conduct problems	
– Infant eczema with sleep problems	3.03 (1.01 - 9.2)
• Hyperactivity	
– Infant Eczema	1.78 (1.02 – 3.09)
– Ever Eczema	2.12 (1.34 – 3.37)

Schmitt J, et al. Allergy 2011;66:404-11

Infant eczema, sleeping problems and mental health at 10 yrs of age

- Sleep disturbance in infant eczema due to itching may be one factor in the development of future mental health problems
- **Clinical Implications**
 - Treat AD aggressively to improve sleep
 - Monitor for sleep disturbance
 - Refer to psychologist or sleep specialist if needed



Schmitt J, et al. Allergy 2011;66:404-11

Atopic Dermatitis: A Practice Parameter Update 2012

Quality of Life and Emotional Stress

- **Summary statement 42.** The clinician should recognize that atopic dermatitis has a significant impact on patient and family quality of life and patients have an **increased risk for psychological distress**. The clinician should ask about stress and emotional factors, which may cause exacerbations and have been found to induce immune activation as well as trigger pruritus and scratching. (C)
- **Summary statement 43.** The clinician should assess for **sleep disturbances**. Sleep may improve with treatment of inflammation, but the clinician may also consider therapeutic agents or referral to a sleep specialist or psychologist in severe cases, or when sleep does not improve in remission. (C)

Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, et al. J Allergy Clin Immunol. 2013 Feb; 131:

Sleep Interventions

- Relaxing, consistent bedtime routine
- Cool temperature
- Wraps or wet underlayer of pajamas
- Sleep-suits/modified pajamas so hands/feet covered
- Treat the inflammation and infection



Chou J et al. Allergy and Asthma Proceedings 2011;32(5):377-83.

Topical Steroid Phobia

- Questionnaire given to AD patients at out-pt dermatology practices (5 university; 53 private practice in France)
- 208 questionnaires (144 parents)
- Results
 - 80.7% fears about topical steroids
 - 36 % admitted non-adherence

Aubert-Wastiaux H, et al. British Journal Dermatology 2011;165:808-814

Topical Steroid Phobia

Dimension	Variable	β -Coefficient (95% CI)	P-value
Fear	Need reassurance	0.67 (0.36–0.99)	< 0.00001
Belief / representation	TCS pass into the bloodstream	0.63 (0.28–0.98)	< 0.001
Origin / communication	Prior adverse event	0.67 (0.03–1.31)	< 0.05
	Discrepancies about quantity	0.34 (0.01–0.66)	< 0.05
Strategy of action	Treat oneself the shortest time possible	0.61 (0.30–0.93)	< 0.001
	Poor adherence	0.53 (0.12–0.94)	< 0.05

Aubert-Wastiaux H, et al. *British Journal of Dermatology* 2011;165:808-814



Boston Children's Hospital Atopic Dermatitis Center

– Multidisciplinary outpatient program for children with refractory AD

– Half day session per week

– Treatment team:

- Nurse Practitioner
- Psychologist
- Nutritionist

www.childrenshospital.org/atopic



Review of BCH AD Center

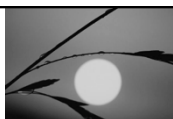
- Overall 71% of patients had improvement in EASI score
- EASI score improvement correlated with:
 - Decreased parental concern with treatment side effects
 - Decreased itching
 - Better patient sleep

Ref. Chou J et al. *Allergy and Asthma Proceedings*. 2011;32(5):377-83.

AD Center – Predictors of clinical success

- Improved parental ability to follow treatment regimen
 - *If the family follows the plan and puts on the meds without worry of side effects the patient will get better*
- Severe AD and younger age of treatment initiation
 - *Patient with severe AD have a greater capacity for improvement*
 - *AD patients tend to improve with time*
 - *Older children have scratching and non-adherence behaviors which are more difficult to change than younger children*

Ref. Chou J et al. *Allergy and Asthma Proceedings*. 2011;32(5):377-83.



Summary

- Skin barrier defects play a role in AD
- Vitamin D induces antimicrobial peptides and may be helpful in AD although more studies are needed
- In patients with frequent flares consider proactive therapy (OFF LABEL)
- Patients with AD (especially severe AD) have an increase in mental health and sleeping disorders